UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/522,602 | 03/17/2005 | Demetrio Manenti | GRT/3687-105 | 3448 |

23117 7590 12/29/2008

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

| EXAMINER | |
|---|---|
| HENRY, MICHAEL C | |
| ART UNIT | PAPER NUMBER |
| 1623 | |
| MAIL DATE | DELIVERY MODE |
| 12/29/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/522,602 | MANENTI ET AL. | |
| | Examiner | Art Unit | |
| | MICHAEL C. HENRY | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *8* is/are allowed.

6)☒ Claim(s) *1-6,9,11-13 and 16-27* is/are rejected.

7)☒ Claim(s) *7,10,14 and 15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/25/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/29/08 has been entered.

The following office action is a responsive to the Amendment filed, 07/29/08.

The amendment filed 07/29/08 affects the application, 10/522,602 as follows:

1. Claims 7, 8, 10, 19-26 have been amended. The rejections made under 35 U.S.C. 103(a) are maintained.
2. The responsive to applicants' arguments is contained herein below.

Claims 1-27 are pending in the application

### *Claim Objections*

Claim 7 is objected to because of the following informalities: The claim recites the words "uracyl, 5,6 dihydrouracyl, 1-methyluracyl, 3-methyluracyl, 5-hydroxymethyluracyl, 2-thiouracyl" which appears to be a typographical error. It appears that the words "uracyl" in each word should be replaced by the word "uracil" since uracyl represents the chemical group and not the heterocyclic compound (uracil) as claimed by applicant. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

> pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 22, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 21, 22, 25 and 26 are drawn to applying or administering a composition, compound or derivative "to a subject" However, the recitation of the language "to a subject" in the claims constitutes new matter as set forth in the claims. More specifically, the specification does not describe, disclose, provide or use any language or matter that pertains to applying or administering any composition "to a subject" as recited in the claims. Furthermore, the introduction of the said language "to a subject" as set forth in claims, constitutes new matter. On the contrary, it should be noted that the specification disclose that the derivative can be applied in cosmetic and pharmaceutical field.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-18, 20, 22, 24-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is indefinite since it is unclear what product or composition is being prepared especially since the claim recites that a derivative is prepared and then the same derivative is "associated with" "at least one organic compound". Furthermore, it is unclear what constitutes

or does not constitute an association or "associating" as recited in the claim. Similarly, Claims 12 and 24 are drawn to said derivative "associated with" a compound. However, the claims are indefinite since it is unclear what constitutes or does not constitute an association. Claim 22 recites the phrase "the method comprising administering said derivative as a pharmaceutical to a subject." However, the claim is indefinite because it is unclear what condition, disorder or disease is being treated by said pharmaceutical composition. It should be noted that the method comprises administration but is unclear what is being treat by said administration. Similarly, Claims 25 and 26 which are drawn to using said derivative as a pharmaceutical is also indefinite because it is unclear what condition, disorder or disease is being treated by said pharmaceutical composition. Also, claims 25 and 26 recite the phrase "cosmetic and/or pharmaceutical". However, the claim is indefinite because it is unclear how the same said composition can be used as a cosmetic and a pharmaceutical simultaneously. Also, Claims 25 and 26 recite the phrase "providing said derivative" However, the claim is indefinite because it is unclear if "providing said derivative" includes or excludes administering or what else the phrase encompasses.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 9, 12, 13, 19, 23, 24, 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over FIDIA SPA (EP 0 555 898 A2).

In claim 1, applicant claims, a derivative formed between hyaluronic acid and at least one heterocyclic compound selected from purine or pyrimidine, said derivative having at least one bond of a ionic type between said acid and said at least one heterocyclic compound. Claims 2-6 are drawn to said derivative wherein the hyaluronic acid is of specific molecular weight. Claim 9 is drawn to said derivative involving specific ionic type between acid and heterocyclic compounds. Claims 12-13 and 27 are drawn to said derivative in association with at least one organic compound and wherein the organic compound is of specific type. Claims 23 and 24 are drawn to cosmetic or pharmaceutical compositions comprising said compounds.

FIDIA SPA discloses a medicament which comprises a partial or stoichiometrically neutral salt of hyaluronic acid with a pharmacologically active substance of a basic nature (aciclovir or acyclovir) (a purine) (see claims 3 and 7; see also abstract). Furthermore, FIDIA SPA discloses that the hyaluronic acid used can have different molecular weights (see page 4, line 35 to page 5, line 31).

The difference between applicant's claimed derivative or composition and the derivative or composition of FIDIA SPA is that FIDIA SPA do not disclose the name of the derivative or compound. However, FIDIA SPA suggests a derivative or compound that read on the claimed invention (see claims 3 and 7; see also abstract).

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made to have prepared any compound suggested by FIDIA SPA such as the neutral salt of hyaluronic acid and a pharmacologically active substance such as acyclovir (a purine), in order to use them to prepare medicaments such as antiviral or anti-tumor medicaments. It should be noted that neutral salt contain at least one ionic bond.

One having ordinary skill in the art would have been motivated, to prepare any compound suggested by FIDIA SPA with a reasonable expectation that the compounds would have the utility suggested by FIDIA SPA. Therefore one skilled in the art would have been motivated to make specific compounds suggested by FIDIA SPA, in order to use them to prepare medicaments such as antiviral or anti-tumor medicaments.

In claim 19, applicant claims a process for the preparation of a derivative formed between hyaluronic acid and at least one heterocyclic compound according to Claim 1, the process comprising reacting at least one carboxyl group of the hyaluronic acid or a salt thereof with at least one amino group of the heterocyclic compound in free or salified form to form at least one ionic bond.

FIDIA SPA discloses a process for the preparation of a derivative between hyaluronic acid and an active substance, characterized in that hyaluronic acid or a salt thereof is made to react with at least one heterocyclic compound in free or salified form. FIDIA SPA discloses that the hyaluronic acid salts with active substances can be prepared wherein all the carboxylic groups of hyaluronic acid may be salified or only a part of the groups are salified. In the partial salts, the remaining carboxylic groups of hyaluronic acid may be free or salified with other active substances (see page 15, lines 21-47). Furthermore, FIDIA SPA discloses the pharmacologically active substance can be the heterocyclic compound, acyclovir (see claims 3 and 7; see also abstract).

The difference between applicant's claimed method and the method of FIDIA SPA is that FIDIA SPA do not exemplify the use of the heterocyclic compound, acyclovir (a purine), per se.

However, FIDIA SPA suggests a method for the preparation of a derivative or compound that read on the claimed invention (see page 15, lines 21-47; see claims 3 and 7; see also abstract).

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made to have used the method of FIDIA SPA to prepare any compound suggested by FIDIA SPA such as the neutral salt of hyaluronic acid and a pharmacologically active substance such as acyclovir, in order to use them to prepare medicaments such as antiviral or anti-tumor medicaments.

One having ordinary skill in the art would have been motivated, to use the method of FIDIA SPA to prepare any compound suggested by FIDIA SPA with a reasonable expectation that the compounds would have the utility suggested by FIDIA SPA. Therefore one skilled in the art would have been motivated to make specific compounds suggested by FIDIA SPA, in order to use them to prepare medicaments such as antiviral or anti-tumor medicaments.

In claim 22, applicant claims a method of using a derivative according to Claim 1, the method comprising administering said derivative as a pharmaceutical to a subject. Claim 25 is drawn to a method of using the composition referred to in Claim 23, the method comprising providing said derivative as a cosmetic and/or pharmaceutical to a subject. Claim 26 is drawn to a method of using the composition referred to in Claim 24, the method comprising providing said derivative as a cosmetic and/or pharmaceutical to a subject.

FIDIA SPA discloses a medicament which comprises a partial or stoichiometrically neutral salt of hyaluronic acid with a pharmacologically active substance of a basic nature (aciclovir or acyclovir) (a purine) (see claims 3 and 7; see also abstract). Furthermore, FIDIA SPA discloses that the medicaments can be used as antiviral or anti-tumor medicaments (see

claims 3 and 7; see also abstract). In addition, it should be noted that the compound aciclovir or acyclovir is one of the most commonly used antiviral.

The difference between applicant's claimed method and the method suggested by FIDIA SPA is that FIDIA SPA do not disclose the name of the derivative or compound. However, FIDIA SPA suggests a derivative or compound that read on the claimed invention (see claims 3 and 7; see also abstract).

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made to have prepared any compound suggested by FIDIA SPA such as the neutral salt of hyaluronic acid and a pharmacologically active substance such as acyclovir (a purine) and to administer it to an individual (as an antiviral or pharmaceutical) in order to treat viral infections such as herpes simplex virus infections in said individual.

One having ordinary skill in the art would have been motivated, to prepare any compound suggested by FIDIA SPA with a reasonable expectation that the compounds would have the utility suggested by FIDIA SPA. Therefore one skilled in the art would have been motivated to make specific compounds suggested by FIDIA SPA such as the neutral salt of hyaluronic acid and a pharmacologically active substance such as acyclovir (a purine) and to administer it to an individual (as an antiviral or pharmaceutical) in order to treat viral infections such as herpes simplex virus infections in said individual.

Claims 1-6, 9, 11, 12, 16, 17, 18, 23, 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bellini et al. (WO 00 01733)

In claim 1, applicant claims, a derivative formed between hyaluronic acid and at least one heterocyclic compound selected from purine or pyrimidine, said derivative having at least one

bond of a ionic type between said acid and said at least one heterocyclic compound. Claims 1-6 are drawn to said derivative wherein the hyaluronic acid is of specific molecular weight. Claim 9 is drawn to said derivative involving specific ionic type between acid and heterocyclic compounds. Claim 11 is drawn to said derivative which is adenine hyaluronate. Claim 12 is drawn to said derivative in association with at least one different organic compound. Claims 16, 17 and 18 are drawn to said derivatives that are cross-linked. Claims 23 and 24 are drawn to cosmetic or pharmaceutical compositions comprising said compounds.

Bellini et al. disclose that the amide derivatives can be obtained by reaction of carboxyl or deacylated nitrogen of hyaluronic acid or a derivative thereof with an amine or with a pharmacologically active acid respectively, or they may be salified or simply associated with said compounds (see page 7, line 3 to page 8, line 14). Furthermore, Bellini et al. disclose that the pharmacologically active compounds can be made to react or be salified with the hyaluronic acid include the heterocyclic compounds adenine, iodouridine and acyclovir (a purine) (see page 7, line 3 to page 8, line 14, especially lines 25-27). In addition, it should be noted that the compound aciclovir or acyclovir is one of the most commonly used antiviral. Also, it should be noted that salified compounds contain at least one ionic bond. Furthermore, Bellini et al. disclose that the hyaluronic acid derivatives can be cross-linked compounds wherein part or all of the carboxyl groups of the D-glucuronic residue form inner or inter-molecular esters with the alcoholic functions of the same polysaccharide chain or other chains respectively.

The difference between applicant's claimed derivative or composition and the derivative or composition of Bellini et al. is that Bellini et al. do not disclose a specific derivative or compound, per se. However, Bellini et al. suggests that hyaluronic acid can be made to react or

salified with pharmacologically active compounds that are anti-virals or anti-tumorals such as the heterocyclic compounds adenine, iodouridine and acyclovir (a purine) to form a hyaluronic acid derivative or compound (see page 7, line 3 to page 8, line 14, especially lines 25-27).

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made to have prepared any compound suggested by Bellini et al. such as the salt of hyaluronic acid and a pharmacologically active substance such as adenine, iodouridine and acyclovir, in order to use them as antiviral or anti-tumor agents.

One having ordinary skill in the art would have been motivated, to prepare any compound suggested by Bellini et al. with a reasonable expectation that the compounds would have the utility suggested by Bellini et al. Therefore one skilled in the art would have been motivated to make specific compounds suggested by Bellini et al., in order to use them as antiviral or anti-tumor agents. It should be noted that the use of hyaluronic acid of different molecular weights depends on factors such as the type or severity of the tumor or viral condition that is to be treated with said derivative or compound.

***Allowable Subject Matter***

The examiner has found claim 8 to be unobvious over the prior art of record and therefore to be allowable over the prior art of record. The examiner has found claim 7 to be unobvious over the prior art of record and therefore may to be allowable provided that the claims objections are overcome. Claims 10, 14, 15 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Though the compound of the present invention are similar to the compounds of the prior art, the compounds of claim 10, 14 and 15 possess

differences (e.g., structural) to the compounds of prior art documents and these differences are not suggested in the prior art, nor are obvious over the prior art.

***Response to Arguments***

Applicant's arguments with respect to claim 1-27 have been considered but are not found convincing.

The applicant argues that FIDIA actually discloses a medicament comprising a pharmaceutically active molecule that can be, for example, hyaluronic acid and adenine arabinoside (i.e., vidarabine). However, FIDIA SPA also discloses a medicament which comprises a partial or stoichiometrically neutral salt of hyaluronic acid with a pharmacologically active substance (aciclovir or acyclovir) (a purine) (see claims 3 and 7; see also abstract). It should also be noted that applicant claimed method (e.g, see applicant's claim 1) does not exclude specific purine (such as acyclovir) or any specific pyrimidine. In fact, applicant's claim 7 recites heterocyclic compounds that include substituted purines and pyrimidines. Furthermore, it should be noted that applicant claims do not require that the heterocyclic compound do not have (or have) pharmaceutical activity.

The applicant argues that by contrast, the present invention relates to derivatives of hyaluronic acid that are formed between hyaluronic acid and a heterocyclic compound derived from purine and/or pyrimidine. See paragraph [0006]. Such heterocyclic compounds are not pharmaceutically active at all and do not have any pharmaceutical activity per se (see Enclosure 5). In particular, the present invention relates to a derivative where the purine and/or pyrimidine compounds are selected from adenine, guanine, thymine, cytosine, and uracyl. However, FIDIA SPA also discloses a medicament which comprises a partial or

stoichiometrically neutral salt of hyaluronic acid with a pharmacologically active substance (aciclovir or acyclovir) (a purine) (see claims 3 and 7; see also abstract). It should also be noted that applicant claimed method (e.g, see applicant's claim 1) does not exclude specific purine (such as acyclovir) or any specific pyrimidine. In fact, applicant's claim 7 recites heterocyclic compounds that include substituted purines and pyrimidines. Furthermore, it should be noted that applicant claims do not require that the heterocyclic compound do not have (or have) pharmaceutical activity.

The applicant argues that in accordance with page 7, lines 3-6, (see above), it is clear that the amide derivatives may be salified or simply associated with pharmacologically active acids. As already discussed above, the present invention does not permit any structural modification of the hyaluronic acid. No covalent bonds are formed between the hyaluronic acid and the purine or pyrimidine base. No amide derivatives are formed reacting the acylated nitrogen of hyaluronic acid. Since no amide derivatives as described in Bellini are formed, the salification product according to the present invention does not correspond to Bellini's salification product. See claim 8 of WO 00/01733. However, applicant's derivative (as claimed) does not exclude hyaluronic acid that is derivatized (such as hyaluronic acid that has an amide group). In fact, in applicant's claims 16-18 the derivatives are cross-linked and the cross-links can involve (e.g., hydroxyl and carboxyl) groups of hyaluronic acid (see claims). Moreover, it should be noted that Claim 1 of Bellini's only requires that only one of R or $R_5$ be an amide group and also recites that $R_5$ can be an $-CO-CH_3$. Consequently, when $R_5$ is $-CO-CH_3$ and R is O- or OH and $R_1, = R_2 = R_3, = R_4 = H$ then the compound is the same as underivatized hyaluronic acid which may be salified with pharmacologically active compounds (see claims 1 and 8 of Bellini).

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Henry whose telephone number is 571-272-0652. The examiner can normally be reached on 8.30am-5pm; Mon-Fri. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael C. Henry
December 17, 2008.

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623